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## **Editorial:** Do depression and stressful events cause premature ageing

Andrew M McIntosh, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh EH10 5HF; Caroline Relton, University of Bristol, Oakfield House, Oakfield Grove, Clifton BS8 2BN

In this issue, Han and colleagues report that depression and childhood trauma are associated with faster ageing in 1130 individuals from the Netherlands Study of Depression and Anxiety (NESDA). What do these findings mean and what do they tell us about major depressive disorder (MDD) and its risk factors?

Han et al exploit a known property of our epigenome, that many differentially methylated regions of our DNA tend to change as we age. These age-sensitive differentially methylated regions can also be used to estimate chronological age, using DNA extracted from various tissues including blood and brain. Whilst your chronological age advances at a fixed rate, your estimated 'DNA methylation age' may advance faster or slower than your age – and many now refer to this ageing estimator as the 'epigenetic clock'(1). A faster clock relative to your chronological age implies acceleration of biological ageing, and this has also been shown to predict age-related diseases and mortality(2). The overwhelming majority of published examples of the 'epigenetic clock' are based on data generated using the Illumina BeadChip platform. However, Han and colleagues have developed a clock using a similar statistical method but data generated from MBD-seq.

Han et al estimated the effect of age on DNA methylation in multiple 'held out' subsets of NESDA, and then used 10-fold cross validation to estimate age in the remaining sample. This process was repeated for all individuals and estimated 'epigenetic age' (EA) was then compared between currently depressed and never-depressed groups.

Individuals with MDD had a higher EA than controls, after correction for multiple potential confounders, albeit the differences were relatively small ( $d = 0.18$ ). These findings replicated in a post-mortem brain collection and the signals generated from both datasets indicated a convergence on neuronal processes. Higher EA was also associated with reports of childhood trauma, a key risk factor for depression in multiple studies.

Han et al's findings suggest that individuals with MDD, and people with histories of childhood trauma, may age biologically relatively faster than unaffected people without traumatic histories. These findings are potentially important, as individuals with MDD or childhood trauma die earlier and have more age-related diseases(3). EA may represent a biomarker of ageing, and therefore a potential mode of stratification of those who may benefit from early interventions seeking to reduce the physical comorbidities of MDD. EA is however more strongly associated with smoking history than MDD(4), and it is not clear whether adjustment for cotinine levels will have dealt adequately with residual confounding by both current and past smoking history.

The study by Han et al also raises several questions about the direction of association and whether depression is causally related to EA acceleration. There are other possible explanations for the observed correlation between these variables, including the possibility

that a shared ‘third risk factor’ or confounder accounts for the observed association. Whilst it seems plausible that MDD ‘causes’ EA acceleration relative to chronological age, the reverse association can also not be ruled out. Various statistical approaches such as Mendelian randomisation or the use of longitudinal data can in theory be helpful in ascribing directionality to a causal relationship. Such methods should be tractable as genome-wide associations studies of MDD and EA become available(5), and more investigators add DNA methylation measures to existing cohorts. It might also be a mistake to assume that greater EA acceleration in MDD is a reflection of ageing, rather than maturation, in the absence of data spanning the life course.

Nevertheless, the findings presented here add MDD and childhood trauma to the growing list of disorders associated with accelerated biological ageing, as defined by the epigenome. These findings provide new routes to discovering their shared mechanisms and reducing multimorbidity and shortened lifespan.

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